

<b>Disease Name</b>	<b>Homocystinuria</b>
<b>Alternate name(s)</b> <b>Acronym</b>	Cystathionine beta-synthase deficiency CBS deficiency
<b>Disease Classification</b>	Amino Acid Disorder
<b>Variants</b>	Yes
<b>Variant name</b>	Pyridoxine-responsive type (the majority of cases are unresponsive to pyridoxine)
<b>Symptom onset</b> <b>Symptoms</b>	Childhood Ectopia lentis, vascular occlusive disease, seizures, malar flush, osteoporosis, possible decreased pigmentation of hair, skin and iris, skeletal abnormalities including genu valgum, pectus excavatum, pes cavus and marfanoid habitus. Some patients have failure to thrive and short stature. Mental retardation is possible.
<b>Natural history without treatment</b>	Mental retardation is common but not invariable. Vascular disease, stroke and psychiatric abnormalities.
<b>Natural history with treatment</b>	Decrease of thromboembolic accidents which may decrease incidence of sequelae including mental retardation, ectopia lentis, seizures and psychiatric abnormalities. Normal IQ is possible and typical of the pyridoxine-responsive variant.
<b>Treatment</b>	Pyridoxine supplementation, dietary restriction of methionine with supplementation of L-cysteine, betaine supplementation. Consider folate and vitamin B12 supplementation.
<b>Emergency Medical Treatment</b>	<b>See sheet from <a href="#">American College of Medical Genetics (attached)</a> or for more information, go to website:</b> <a href="http://www.acmg.net/StaticContent/ACT/Methionine.pdf">http://www.acmg.net/StaticContent/ACT/Methionine.pdf</a>
<b>Physical phenotype</b>	Ectopia lentis, decreased pigmentation, malar flush, osteoporosis, skeletal abnormalities and marfanoid habitus
<b>Inheritance</b>	Autosomal recessive
<b>General population incidence</b>	1:200,000 – 300,000
<b>Ethnic differences</b>	Yes
<b>Population</b>	Irish, U.S New England
<b>Ethnic incidence</b>	1:50,000
<b>Enzyme location</b> <b>Enzyme Function</b>	Lymphocytes, fibroblasts and liver Degradation of homocysteine
<b>Missing Enzyme</b> <b>Metabolite changes</b>	Cystathionine beta-synthase Increased methionine in blood, increased homocystine in urine, increased total homocysteine in blood.
<b>Prenatal testing</b>	Enzyme assay in cultured amniocytes (CVS not possible)
<b>OMIM Link</b>	<a href="http://www.ncbi.nlm.nih.gov/omim/236200">http://www.ncbi.nlm.nih.gov/omim/236200</a>
<b>Genetests Link</b>	<a href="http://www.genetests.org">www.genetests.org</a>
<b>Support Group</b>	National Coalition for PKU and Allied Disorders <a href="http://www.pku-allieddisorders.org/">http://www.pku-allieddisorders.org/</a> Children Living with Inherited Metabolic Diseases <a href="http://www.climb.org.uk/">http://www.climb.org.uk/</a>

## Newborn Screening ACT Sheet [Increased Methionine] Homocystinuria (CBS Deficiency)

**Differential Diagnosis:** Classical homocystinuria (cystathionine  $\beta$ -synthase (CBS) deficiency); hypermethioninemia due to methionine adenosyltransferase I/III (MAT I/III) deficiency; glycine N-methyltransferase (GNMT) deficiency; adenosylhomocysteine hydrolase deficiency; liver disease; hyperalimentation.

**Condition Description:** Methionine from ingested protein is normally converted to homocysteine. In classical homocystinuria due to CBS deficiency, homocysteine cannot be converted to cystathionine. As a result, the concentration of homocysteine and its precursor, methionine, will become elevated. In MAT I/III deficiency and the other hypermethioninemias, methionine is increased in the absence of or only with a slightly increased level of homocysteine.

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### YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn with attention to liver disease and refer as appropriate.
- Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- Educate family about homocystinuria and its management, as appropriate.
- Report findings to newborn screening program.

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**Diagnostic Evaluation:** Quantitative plasma amino acids will show increased homocystine and methionine in classical homocystinuria but only increased methionine in the other disorders. Plasma homocysteine analysis will show markedly increased homocysteine in classical homocystinuria and normal or only slightly increased homocysteine in the other disorders. Urine homocysteine is markedly increased in classical homocystinuria.

**Clinical Considerations:** Homocystinuria is usually asymptomatic in the neonate. If untreated, these children eventually develop mental retardation, ectopia lentis, a marfanoid appearance including arachnodactyly, osteoporosis, other skeletal deformities and thromboembolism. MAT I/III deficiency may be benign. Adenosylhomocysteine hydrolase deficiency has been associated with developmental delay and hypotonia, and both this disorder and GNMT deficiency can cause liver abnormalities.

### Additional Information:

[Gene Reviews](#)

[Genetics Home Reference](#)

### Referral (local, state, regional and national):

[Testing](#)

[Clinical Services](#)

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

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